REMARKS

Claims 1, 2, 9-13 and 16-20 are pending in the application. Support for the amendment to claims 16 and 18 can be found throughout the application, and in particular on page 1, lines 12 and 13; page 5, lines 5, 6, and 26; and page 14, line 17.

Examiner also noted that applicant stated that claims 1, 9-13, and 16-20 were pending and noted that claim 2 had not been cancelled. Applicants would like to clarify that claim 2 is pending and should have been included in the list of pending claims.

Obvious-Type Double Patenting

Claims 1-2, 9-13, and 20 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,340,746 B1. In response, Applicants submit a Terminal Disclaimer along with the fee required under 37 C.F.R. §§ 1.312(c). Applicants believe that this timely filed terminal disclaimer overcomes the non-statutory double patenting rejection.

Rejections Under 35 U.S.C. §112

Claims 2 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 was rejected because the term "derived from" was allegedly unclear. Applicants respectfully traverse. Claim 2 has been amended to removed "derived from." Removal of this rejection is therefore respectfully requested.

In regard to claim 16, Examiner states that the claim is indefinite in that it is not clear to whom the prodrug is being administered. Applicants respectfully traverse. Claim 16 has been amended to recite that the prodrug is being administered to a mammal. Applicant respectfully

requests the removal of this rejection.

Claims 16 and 18 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. The Examiner alleges that the specification fails to teach what is encompassed by the terminology "toxic insult" and what its causes are. The Examiner further alleges that the specification fails to teach the mode of administration and an effective amount of the active ingredient.

Applicant respectfully traverses the rejection. Claims 16 and 18 have been amended to recite that the toxicity of a substance is reduced in a mammal. Amendments to claim 16 and 18 merely clarify the invention and were not made for reasons of patentability. In other words, the phrase "toxicity of a substance" is synonymous with "toxic insult" and is not intended to be a narrowing amendment. The phrase "toxicity of a substance" is well known in the art and encompasses substances that causes toxicity in a mammal. The specification is replete with examples of toxic substances. For example, page 2, lines 2-7 of the specification teaches one of ordinary skill in the art that toxic electrophiles, free radicals, chemotherapy, acrolein, and radiation all cause toxicity and are therefore all considered toxic substances. Page 4, line 1 of the specification teaches that AIDS is a toxic substance. Page 6, line 8 of the specification also teaches that hepatotoxins are toxic substances. Page 14, line 17 teaches cysteamine is a toxic substance. Therefore, the meaning of "toxicity of a substance" would have been clear to one of ordinary skill in the art.

The Examiner also alleges that the specification fails to teach a mode of administration and an effective amount of the active ingredient. Applicants respectfully traverse. As stated in the specification at page 7, lines 10-17:

Novel thio- and selenol- containing compounds overcome several

problems facing the art, including toxicity, water-solubility, and lack of target specificity. First, the protective or preventive activity and clinical utility will be greatly enchanced by converting the cysteine, cysteamine, glutathione, selenocysteine, selenocysteamine, and WR compounds, to thiazolidine and selenazolidine prodrug forms. These prodrugs provide a slow release form of the thiol/selenol-amine, which greatly reduces observed toxicity (with related compounds), but provides the active agent after enzymatic or non-enzymatic biotransformation.

The administration of thio-, selenol, and related compounds to treat toxicity was well known in the art prior to the priority date of the present invention. The novel and unobvious compounds disclosed in the specification are derivatives and prodrugs of the thio- and selenol compounds, described above, which have the same effects as these compounds without the toxic side effects. Therefore, the mode of administration and dosage of the compounds claimed herein are generally similar if not identical to the modes of administration and dosages of the compounds known in the art. Therefore, one skilled in the art would have been apprised of how to administer the compounds of the invention as well as the effective amounts of these compounds.

For example, El-Bayoumy *et al.* (J. Cell. Biochem., Supp. 22:92-100, 1995) (Exhibit A) discloses cancer prevention by organoselenium compounds such as 1,4-phenylenebis(methylene)selenocyanate (p-XSC). In Table 1, p-XSC is given in concentrations of 5, 10, and 15 ppm. Each consecutively higher dose shows a marked decrease in total tumor yield. El-Bayoumy also discusses dosages for selenium and notes that levels above 5 ppm are toxic (p. 93) and uses a dosage of 3 ppm as a control (Table 1). It is also worthy to note that El-Bayoumy

teaches the "chemopreventative index," which is calculated by obtaining the ratio of maximum tolerable dose to the effective dose which produced approximately 50% inhibition in total tumor yield. This formula allows for one of ordinary skill in the art to calculate an effective dosage to inhibit tumor growth. El-Bayoumy also teaches that effective modes of administration include diet or drinking water (page 93). Therefore, one of ordinary skill in the art would have been able to easily assess effective dosages and routes of administration for the claimed prodrugs.

Examiner also rejected claims 17 and 19 under 35 U.S.C. §112, first paragraph, for lack of enablement. The Examiner states that on page 1 of the specification the uses set forth in claims 17 and 19 are potential, and according to the Examiner, the uses set forth in the claims are merely speculative and would require further research and an undue amount of experimentation to determine which uses are credible. The Examiner further alleges that the specification fails to set forth any evidence that the claimed methods have the uses as claimed and fails to teach a mode of administration and an effective amount of the active ingredient.

Applicants respectfully traverse this rejection. The administration of thio- compounds and selenium to treat those conditions recited in claims 17 and 19 was well known in the art prior to the priority date of the present invention. The novel and unobvious selenium compounds disclosed and claimed in the present invention are derivatives and prodrugs of compounds known in the art for teaching the maladies recited in claims 17 and 19. While the selenium compounds in the present invention can treat these maladies, they have the added benefit of being less toxic than their corresponding compounds known in the art. Furthermore, the mode of administration and dosage of the selenium compounds claimed herein are generally similar if not identical to the modes of administration and dosages of the thiol compounds known in the art. Therefore, one skilled in the art would have been apprised of how to administer the compounds

of the invention as well as the effective amounts of these compounds.

Specifically, the first use recited in claims 17 and 19 is reducing unwanted side effects of chemo- or radiotherapy of cancer. Tamba et al. (Z Naturforsch, 44:857-62, 1989) discloses thiols such as thiyl radicals derived from glutathione, cysteine, penicillamine, and 2-mercaptoethanol (abstract). Importantly, Tamba et al. discloses "The importance of sulphur compounds as modifiers of radiation response dates almost 40 years ago, when it was observed that the presence of some exogenous thiols at the time of irradiation resulted in protection of biological systems *in vitro* as well as of animals *in vivo*. Numerous compounds with radioprotective potential, mainly sulfur containing, have since been designed, synthesized, and tested *in vitro* and *in vivo* systems." (page 857, first paragraph.)

Bohm et al. (Cancer Res. 11:1613-1616, 1991) shows that glutathione protects against cisplatin-induced renal toxicity without reducing the antitumor activity of the cytotoxic agent, along with effective dosages and methods of administration (p. 1614).

Furthermore, Kumar et al. (Pharm. Ther. 39:301-309, 1988) disclose that glutathione affords radioprotection (abstract), and Yarbo et al. (Sem. Oncol, 18(1):48-58, Supp. 2, 1991) disclose that sulfur-containing nucleophiles such as sodium thiosulfate are chemoprotectants for cancer chemotherapy (abstract.) Yarbo also discloses on page 52, left column that:

> Several other thiol-based compounds have shown activity in preventing cisplatin-induced toxicities. These include the experimental aminothiol WR-2721, the disulfide metal chelator diethyldithiocarbamate (DDTC), mesna, N-acetylcysteine, and thiourea. While some of these agents have only been evaluated in animal models (mesna, thiourea), DDTC has been found to be an effective chemoprotectant for the kidney in patients

receiving either cisplatin or carboplatin." Yarbo goes on to disclose effective dosages for chemoprotection.

Therefore, one of ordinary skill in the art would have been apprised of how to administer the selenium compounds of the invention as well as the effective amounts of these compounds as chemo- and radioprotectants based upon what was well known in the art with respect to the administration of thiol compounds.

The second use recited in claims 17 and 19 is improving cardiovascular function. Steare et al. (J Mol Cell Cardiol 27:65-74, 1995) discloses that reactive oxygen species (free radicals) are generated during ischemia-reperfusion of the myocardium (heart), and can contribute to the pathophysiology of the heart. Steare et al. reviews the role of endogenous antioxidant systems in protection of the myocardium against ischemia-reperfusion and discusses the evidence that alterations in endogenous antioxidant status can provide protection of the heart to reversible and lethal cellular injury (abstract). Steare et al. shows the role of glutathione in the defense against the "oxidant stress of ischemia-reperfusion injury" (p. 65). Also discussed is that cellular levels of glutathione can be increased by administering glutathione itself or cysteine precursors (p. 70). Therefore, based on the disclosure in Steare et al. for administering thiol compounds tfor preventing damage to the myocardium, one of ordinary skill in the art would have been apprised of how to administer the selenium compounds of the invention as well as the effective amounts of these compounds to improve cardiovascular function.

Claims 17 and 19 recite the use of preventing mutagenesis, preventing the initiation and/or progression of cancer, reducing toxic consequences of planned or unplanned radiation or chemical exposures, and slowing the aging process. Bezlepkin et al. (Mech. Aging Devel. 92:227-234, 1996) teaches one of ordinary skill in the art that there is abundant evidence that the

lesions in DNA, proteins and lipids and their accumulation with age can be responsible for cancer and various pathologies, and that this occurrence is caused by oxidative damage. Bezlepkin et al. show that selenium can reduce oxidative damage *in vivo* and, therefore, prevent the initiation and progression of cancer as well as reduce toxic consequences of radiation or chemical exposures, which cause oxidation (p. 229).

Crary et al. (Med. Hypotheses 13:77-98, 1994), disclose that "High but well tolerated doses of...selenium...have significant immunostimulant, anti-inflammatory, and anti-carcinogenic effects which are well documented in the existing biomedical literature. In addition, these antioxidants help to protect the structural integrity of ischemic or hypoxic tissues, and may have useful anti-thrombotic actions as well." (abstract). Crary goes on to say on page 81 that:

> Selenium is the most potent broad-spectrum anti-carcinogenic agent that has yet been discovered. When added to food or water at 1-4 ppm, selenium has offered protection against a wide variety of carcinogens in animal models of carcinogenesis. Supplementary selenium has reduced the incidence of liver cancer in animals treated with AAF, or 3MeDAB, or colon cancer induced with DMH or MAM, of skin papillomas induced with DMBA, BP, and MCA, and of mammary tumors induced with DMBA...Supplementary selenium has also substantially reduced the incidence of incidence of 'spontaneous' mammary tumors in C3H mice; in one such study, a 10% life-long incidence of mammary tumors in selenium-treated mice contrasted with an 82% incidence in untreated controls.

Therefore, one of ordinary skill in the art would have been apprised of how to administer the selenium compounds of the invention as well as the effective amounts of these compounds for preventing mutagenesis, preventing the initiation and/or progression of cancer, reducing toxic consequences of planned or unplanned radiation or chemical exposures, and slowing the aging process, based on the teachings in the art.

The final use recited in claims 17 and 19 is preventing cataract formation in a mammal. Cai et al. (Biomed. Environ. Sci, 7:109-115, 1994) disclose that selenium deficiency can be involved in the occurrence of cataracts. "The results showed that the decrease of antioxidative capability in the lenses of [selenium deficient]...rats accelerated the lipid peroxidation and generation of free radicals." (Abstract.) They also disclose that it has been known in the art since 1971 that selenium concentration in the lens of patients suffering from cataract decreased 1/6 in the normal lens (p. 109). Therefore, one of ordinary skill in the art would have been apprised of how to administer the selenium compounds of the invention to prevent cataract formation, based on the teachings in the art.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $290.00 ($55.00 for the Terminal Disclaimer Fee, $55.00 for the extension of time fee, and $180.00 for the Information Disclosure Statement) is enclosed. This amount is believed to be correct;

however, the Commissioner is hereby authorized to charge any additional fees, which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

Lawrence A. Villanueva
Registration No. 43,968

NEEDLE & ROSENBERG, P.C.
Customer No. 23859
678/420-9300 (Phone\
678-420-9301 (Fax)

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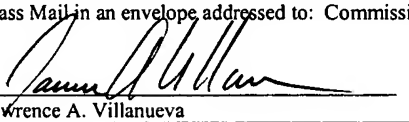

Lawrence A. Villanueva

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